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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 11/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/700,273	KLINGLER ET AL.	
	Examiner	Art Unit	
	Venkataraman Balasubramanian	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-12 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-12 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 11/3/2005.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-12 are pending.

Information Disclosure Statement

References cited in the Information Disclosure Statement, filed on11/3/2003, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Any claim not specifically rejected is rejected as it is dependent claim on a rejected claim and shares the same indefiniteness.

1. Claim 1 is indefinite as it is not clear whether it is a compound claim or a composition claim. The first line of the claim recites a compound and the line before the proviso at the end of the claim recites "and pharmaceutically acceptable carrier" which makes claim 1 both a compound and composition claim. Hence, claim 1 and its dependent claims 2-12 are indefinite.
2. Recitation of "provided that the unsubstituted benzo[1,3]dioxole is excluded" in the end of claim is vague and unclear as what is intended.
3. Claim 7 is indefinite as it is not clear whether it is process of producing a pharmaceutical or method of use of the compound of claim 1 for treating a disease. If the claim 7 is a process of making pharmaceutical , it is indefinite as it

omits the essential steps . If it is meant to be a method of treating, the recitation of process of producing clearly would render the claim indefinite. Again as recited claim 7 appears to be a process claim as well as a method of use claim.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for osteoarthritis, does not reasonably provide enablement for treating nay or all disease generically embraced in the claims 7-8 and more specifically in claims 9-12. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Following apply.

The instant method of use claim 3 is a Reach through Claim. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions for which they lack written description and enabling disclosure in the specification.

In the instant case, it appears that, because the instant compounds inhibit angiogenesis which are said to be present in cancer, it is implied that, based on cell inhibition of angiogenesis, any or all cancer can be treated with the instant compounds for which there is no adequate written description and enabling disclosure. The instant method of use claim 7 is drawn to "treating a MMP-13 associated disorder in general. The scope of the claims includes any or all disorders, mediated by MMP-13 including

those yet to be discovered as due said mode of action for which there is no enabling disclosure. The instant compounds are disclosed to have inhibitory activity toward MMP-13 and it is recited (page 42 and 73-74) that as a result of their pharmacological properties, the compounds of the formula I are suitable for the prophylaxis and therapy of all those diseases in whose course an increase in the activity of matrix metalloproteinase 13 is involved. These diseases include degenerative joint diseases, such as osteoarthroses, spondyloses or cartilage loss following joint trauma or a relatively long period of joint immobilization following meniscus injuries or patella injuries or ligament rupture. They also include:) diseases of the connective tissue such as collagenoses, periodontal diseases, wound healing disturbances and chronic diseases of the locomotory apparatus, such as inflammatory, immunologically determined or metabolism-determined, acute and chronic authorities, arthropathies, myalgias and disturbances of bone metabolism or cancer diseases such as breast cancer for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action that would be useful for all sorts of disorders and diseases. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host.

The term " prophylaxis" actually means to prevent spread of a disease (as per Meriam Webster's Dictionary) and there is no disclosure as to how one skilled in the art can reasonably establish the basis and the type of subject to which the instant compounds can be administered in order to have the "prevention" effect. There is no

evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein.

Moreover many if not most of diseases such as psoriasis, multiple sclerosis, tumors , autoimmune diseases etc are very difficult to treat and despite the fact that there are many drugs, which can be used for "inflammatory condition".

The scope of the claims involves all of the thousands of compounds of claim 1 as well as the thousand of diseases embraced by the terms, inflammation, and autoimmune disease.

Cancer is just an umbrella term. Tumors vary from those so benign that they are never treated to those so virulent that all present therapy is useless.

Inflammation is a process that can take place in virtually any part of the body. There is a vast range of forms that it can take, causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There is no common mechanism by which all, or even most, inflammations arise. Mediators include bradykinin, serotonin, C3a, C5a, histamine, leukotrienes, cytokines, and many, many others. Accordingly, treatments for inflammation are normally tailored to the particular type of inflammation present, as there is no, and there can be no "magic bullet" against inflammation generally.

The "autoimmune diseases" are a process that can take place in virtually any part of the body. There is a vast range of forms that it can take,' causes for the problem, and biochemical pathways that mediate the inflammatory reaction. There are hundreds

such diseases, which have fundamentally different mechanisms and different underlying causes. Thus, the scope of claims is extremely broad.

No compound has ever been found to treat cancer of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different organs and have different methods of growth and harm to the body. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally. Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art is indicative of the requirement for undue experimentation. See Hoekstra et al. The

Oncologist, 6:415-427, 2001 and Poole et al. Biochem. Soc. Symp. 70:115-123, 2003 (PubMed Abstract provided).

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: Therapeutic use of the compounds in treating disorders/diseases that require MMP-13 inhibitory activity.

2) The state of the prior art: Recent publications expressed that the MMP-13 inhibition effects are unpredictable and are still exploratory. See Hoekstra et al. and Poole et al. cited above.

3) The predictability or lack thereof in the art: Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for r treating any or all condition of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples: Specification has no working examples to show treating any or all

condition and the state of the art is that the effects of MMP-13 inhibitors are unpredictable.

6) The breadth of the claims: The instant claims embrace any or all inflammatory disorders and various diseases including autoimmune diseases such as HIV, multiple sclerosis diseases and tumors including those yet to be related to MMP-13.

7) The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds towards treating the variety of diseases of the instant claim, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion

is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 5-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Barvian et al., WO 02/064571.

Barvian et al., teaches several pyrimidine derivatives as matrix metalloproteinase inhibitors, which include the compounds, composition and the method of use embraced in the instant claims. See formula I, page 3 and note the definition of A, B and R^2. Note when R^2 is hydrogen and A and B are second choices provided therein, the compounds taught by Barvian et al., include instant compounds. See formula III and V, pages 4-5. See pages 5-7 for various species of compounds which include instant compounds. See pages 16-23 for the process of making including Scheme I and Scheme 2. See also pages 22-25 for composition and method of use.

Claims 1-3 and 5-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Baader et al., US 5,130,317.

Baader et al. teaches pyrimidine-4,6-dicarboxylic acid diamides useful as immunosuppressants, which include instant compounds, process and pharmaceutical composition. See Formula I and note the definition of R^1 and R^2. Note when R^1 is alkyl

further substituted with phenyl, or indolyl, the compounds taught by Baader et al. include instant compound when instant R2 is alkyl substituted with phenyl or Het as permitted by choice 4.35 or choice 4.34. See entire document, especially example 2.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable by Barvian et al., WO 02/064571.

Teachings of Barvian et al. as discussed in the above 102 rejection is incorporated herein. As noted above, Barvian et al., teaches several pyrimidine derivatives as matrix metalloproteinase inhibitors, which include the compounds, composition and the method of use embraced in the instant claims. See formula I, page 3 and note the definition of A, B and R^2. Note when R^2 is hydrogen and A and B are second choices provided therein, the compounds taught by Barvian et al., include instant compounds.

Barvian et al exemplifies a limited number of compounds from the genus embraced in formula I, III and V. Thus Barvian differs in not exemplifying all compounds of the genus which broadly embrace the instant genus.

However, Barvian et al. teaches the equivalency of those compounds exemplified with specific substituents with that generically recited for Formula I or III or V as seen in pages 3-11. Note the choices for variables include several compounds, which are generically claimed in the instant claims.

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make variously substituted pyrimidine compounds of formula I, III or V as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Claims 1-12 are rejected under 35 U.S.C. 103(a) as being unpatentable by

Baader et al., US 5,130,317.

Teachings of Baader et al. as discussed in the above 102 rejection is incorporated herein. As noted above, Baader et al. teaches pyrimidine-4,6-dicarboxylic acid diamides useful as immunosuppressants, which include instant compounds, process and pharmaceutical composition. See Formula I and note the definition of R^1 and R^2. However, Baader et al exemplifies a limited number of compounds from the genus embraced in formula I. Thus, Baader et al., differs in not exemplifying all compounds of the genus which broadly embrace the instant genus.

However, Baader et al. teaches the equivalency of those compounds exemplified with specific substituents with that generically recited for Formula I as seen column 2. Note the choices for variables include several compounds, which are generically claimed in the instant claims.

Thus, it would have been obvious to one having ordinary skill in the art at the time of the invention was made to make variously substituted pyrimidine compounds of formula I, as permitted by the reference and expect resulting compounds (instant compounds) to possess the uses taught by the art in view of the equivalency teaching outline above.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., In re Berg, 140

F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); In re Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); In re Longi, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); In re Van Ornum, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); In re Vogel, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In re Thorington, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-12 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-17 of U.S. Patent No. 6,913,298. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter namely pyrimidine dicarboxamides, composition and the method of use embraced in the instant claims overlap with those embraced in the commonly assigned US patent 6,933,298 .

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661.

The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of

this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAG. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-2 17-9197 (toll-free).

Venkataraman Balasubramanian

11/19/2005